Office Action Summary	Application No.	Applicant(s)	
	09/445,289	MUKAMOLOVA ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *126-128,131,135-139,144,149-157 and 159-164* is/are pending in the application.

4a) Of the above claim(s) *135-139 and 151-156* is/are withdrawn from consideration.

5)☒ Claim(s) *160* is/are allowed.

6)☒ Claim(s) *126-128,131,144,149,150,157,159 and 161-164* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *110210*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 06/07/10 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 07/13/10 and 06/07/10 in response to the advisory action mailed 05/18/10 and the final Office Action mailed 01/05/10.

Status of Claims

3) Claims 126, 128, 144, 148 and 149 have been amended via the amendment filed 07/13/10.

Claims 148 and 158 has been canceled via the amendment filed 07/13/10.

New claims 160-164 have been added via the amendment filed 07/13/10.

Claims 126-128, 131, 135-139, 144, 149-157 and 159-164 are pending.

Claims 126-128, 131, 144, 149, 150, 157 and 159-164 are under examination.

Attempted Interview

4) Attempts were made by the Office to have a discussion with Applicants' representative on the amendments filed 07/13/10 and 06/07/10. A telephonic message was left to the attorney of record, Melissa Hunter-Ensor, on 11/02/2010 after her stated return from leave. A request was made to call the Examiner of record back as soon as possible so that Applicants' most recent amendment can be

discussed. The Office has not heard from the attorney of record as of the issuance of this Office Action.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action References.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

7) The objection to the specification made in paragraph made in paragraph 23(b) of the Office Action mailed 01/06/09 and maintained in paragraph 10 of the Office Action mailed 01/05/10 with regard to claim 144 is withdrawn in light of Applicants' amendment to the claim.

Objection(s) Maintained

8) The objection to the specification made in paragraph made in paragraph 11 of the Office Action mailed 01/05/10 with regard to claim 128 is maintained for the reasons set forth therein. It is noted that Appellants have not addressed this issue.

Rejection(s) Moot

9) The rejection of claim 158 made in paragraph 20(b) of the Office Action mailed 01/06/09 and maintained in paragraph 24 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

10) The rejection of claims 148 and 158 made in paragraph 26 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 148 and 158 made in paragraph 27 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claim 158 made in paragraph 29 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

13) The rejection of claim 128 made in paragraph 29(b) of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn. A new rejection is set forth below to address the claim as amended.

14) The rejection of claim 144 made in paragraph 29(c) of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

15) The rejection of claims 126-128, 131, 144, 149, 150, 157 and 159 made in paragraph 26 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the claims and/or the base claim. Applicants' arguments have been considered, but are moot in light of the withdrawal of the rejection.

Rejection(s) Maintained

16) The rejection of claim 128 made in paragraph 29(a) of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein. Other than stating that the rejection is overcome by the present amendment, Applicants have not advanced any substantive arguments. The amendment does not overcome the rejection.

17) The rejection of claim 159 made in paragraph 29(c) of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reason set forth therein.

18) The rejection of claims 126-128, 131, 144, 149, 150, 157 and 159 made in paragraph 27 of the Office Action mailed 01/05/10 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is maintained for the reasons set forth therein and herein below. The rejection is still applicable to claims as amended, including the amended claim 128.

Applicants mention about the interview dated 06/29/10 and acknowledge that *M. luteus* and *M. tuberculosis* polypeptides share *less than* 95% identity as shown in Figure 1A. Applicants point to page 48, line 24 to page 49, line 21; page 52, line 6 to page 53, line 11; page 57, line 16 to page 59, line 19 and state that both proteins share similar cell growth promoting activity. Applicants assert that the specification describes a number of polypeptides having various degrees of identity to SEQ ID NO: 2, including RP-factors of *M. tuberculosis* and *M. luteus.* Applicants argue that in view of this finding, one of skill in the art would expect that proteins having a higher degree of identity to SEQ ID NO: 2 would also promote the growth of dormant cells. Applicants assert that once provided with SEQ ID NO: 2, one of skill in the art could readily identify proteins having at least

95% identity to that sequence. Applicants cite MPEP 2163.04 II. A.3(a) and state that an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the Applicants had possession of the claimed invention and that Applicants' specification clearly satisfies the written description requirement. Applicants point to page 50, line 9 to page 51, line 6 under the header "Identification of RP-factor homologues" and state that using sequence information relating to *M. luteus* RP-factor, Applicants have identified RP factor proteins from other bacteria, including SEQ ID NO:2 from *M. tuberculosis,* that share sequence identity with *M. luteus* RP-factor. Applicants point to page 50, lines 22-25 and page 51, lines 2-6 of the specification and submit that they have used the sequence information obtained from *M. luteus* to identify related RP-factors in a number of other organisms, including *M. tuberculosis, M. leprae, Streptomyces rimosus, M. smegmatis, M. bovis,* and *Corynebacterium glutamicum.* Applicants further submit the following: Applicants have provided an alignment of RP factor proteins in Figure 1A, which identifies conserved structural features and highly conserved amino acid residues (page 51, line 7 to page 52, line 2, under the heading "Domain structure"; Figures 9A and 9B). Applicants found that RP-factors share a secretory signal sequence and a conserved 70-residue segment that may act as a signaling domain (page 51, lines 10-12). This domain includes four conserved tryptophan residues and two conserved cysteine residues that may form a disulfide bridge (page 51, lines 27-28 and page 52, lines 1 and 2). These structural features are conserved among a wide variety of proteins and are, therefore, *likely to be* functionally important. In view of this disclosure, Applicants' specification clearly provides guidance relating to those regions of the protein where sequence variations are likely to be tolerated and those conserved regions

where variations in the sequence are less desirable (see also, page 10, line 11, to page 17, line 10).

Applicants further state that one of skill in the art could readily identify those variant polypeptides that fall within the scope of Applicants' claims (i.e., those polypeptides having at least 95% amino acid sequence identity to SEQ ID NO: 2 that are capable of resuscitating a dormant, moribund, or latent *Mycobacterium tuberculosis* cell) using routine methods that are described in Applicants' specification. Applicants state that their specification clearly describes methods of screening for polypeptides capable of resuscitating dormant bacteria using *purified* RP-factors (page 48, line 24, to page 49, line 21, and page *52-53,* under the heading "RP Factor Activity") and that such screening could easily be accomplished using standard techniques that are plainly described in Applicants' specification. Applicants contend that they have expressed a secreted form of the *M. tuberculosis* polypeptide, SEQ ID NO: 2, in *E. coli* (page 54, line 4, to page 57, line 27) which included amino acids beginning at D50 of the amino acid sequence and included amino acids 117-184 as recited in the claims (page 57, lines 16-25). The *purified* protein was added to cultures of M. *luteus* and *M. tuberculosis.* Applicants found that as expected SEQ ID NO: 2 stimulated the growth of *M. tuberculosis* cells and *M. luteus* cells (page 57, line 16-line 27). Applicants found that the control culture grew to a final OD600nm of 1.0 (page 57, lines 25-27). In contrast, cultures treated with purified RP-factor continued to grow to final OD600nm of 2.0-6.0 (page 57, lines 25-27). These results indicated that a SEQ ID NO: 2 polypeptide containing amino acids 117-184 was capable of resuscitating a dormant, moribund, or latent *Mycobacterium tuberculosis* cell under conditions where the control culture failed to grow. Applicants assert that they have described a number of polypeptide variants, have described a correlation between

structure and function, and have described methods for identifying polypeptides having the desired biological activity, which establishes that Applicants had possession of the invention as claimed.

Applicants' arguments have been carefully considered, but are not persuasive.

The Office agrees with Applicants that an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the Applicants had possession of the claimed invention. However, as set forth previously, possession of a representative number of polypeptide species falling within the scope of the genus may *not* be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

It was indicated during the telephonic interview of 06/29/10 that none of the sequences depicted in Figure 1A are not 95% identical to the instantly recited SEQ ID NO: 2. Applicants' current acknowledgement that *M. luteus* and M. *tuberculosis* share less than 95% identity as shown in Figure 1A, has been noted. This establishes that the structure of the sequence species from Figure 1A is excluded from the scope of the at least 95% identical polypeptide variants recited in the instant claims.

Whether or not purified SEQ ID NO: 2 comprises therein amino acid residues 117 to 184 of SEQ ID NO: 2 is not the issue. However, whether or not a purified or non-purified polypeptide having up to 5% non-identity with SEQ ID NO: 2, i.e., having amino acid substitutions, additions, deletions and/or insertions, any where along the length of SEQ ID NO: 2, as long as it retains at least 95%,

96%, 97%, 98% and 99% sequence identity thereto, would have the requisite ability (1) to resuscitate dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in a human or animal sample, and/or (2) also identify a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in said human or animal sample by detecting its growth, is the issue. Whether or not the single purified SEQ ID NO: 2 species comprising therein amino acid residues 117 to 184 of SEQ ID NO: 2 stimulated the growth of *M. tuberculosis* cells and *M. luteus* cells, is not the issue. However, that a purified or non-purified polypeptide having at least 95%, 96%, 97%, 98% and 99% sequence identity thereto, or having amino acid residues 117 to 184 of SEQ ID NO: 2, would not retain both of the requisite functions, is the issue. This is important because the only two purified polypeptide species that have been evaluated for their ability to resuscitate dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in a culture medium, let alone identify such cells, upon contacting and incubation as recited, are *M. luteus* RPf polypeptide and *Mycobacterium tuberculosis* RPf2 polypeptide. See Figure 10. Not only *M. luteus* and *M. tuberculosis* polypeptides share *less than* 95% identity as acknowledged by Applicants, the two polypeptide are of very diverse structure. See the sequence alignment below.

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APPLICATION NUMBER: 09/445,289
APPLICANT: MUKAMOLOVA, GALINA V.
APPLICANT:KAPRELYANTS, ARSENY S.
APPLICANT:YOUNG, DANIELLE I.
APPLICANT:KELL, DOUGLAS B.
APPLICANT:YOUNG, MICHAEL
TITLE OF INVENTION: BACTERIAL PHEROMONES AND USES THEREFOR
PRIOR APPLICATION NUMBER: 09/445,289
PRIOR FILING DATE: 2000-05-11
PRIOR APPLICATION NUMBER: PCT/GB98/01619
PRIOR FILING DATE: 1998-06-03
PRIOR APPLICATION NUMBER: GB 9711389.8
PRIOR FILING DATE: 1997-06-04
PRIOR APPLICATION NUMBER: GB 9811221.2
PRIOR FILING DATE: 1998-05-27
SOFTWARE: PatentIn Ver. 3.3
SEQ ID NO 36
LENGTH: 220
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TYPE: PRT
ORGANISM: Micrococcus luteus

  Query Match             22.9%;  Score 232.5;  DB 7;  Length 220;
  Best Local Similarity   35.7%;
  Matches   56;  Conservative   15;  Mismatches  41;  Indels   45;  Gaps  3.

Qy          32 TLVTTSPAGIAHADDAGLDPNAAAGPDAVGFDPNLPPAP-DAAPVDTPPAPEDAGFDPNL 90
               || |||      |  : :     ||  ||||      ||  || |||
Db           2 TLFTTSATRSRRATASIVAGMTLAGAAAVGFS-----APAQAATVDT------------ 43

Qy          91 PPPLAPDFLSPPAEEAPPVPVAYSVNWDAIAQCESGGNWSINTGNGYYGGLRFTAGTWRA 150
                                          || :|:||| | | ||||||:|||::||  :|:|
Db          44 --------------------------WDRLAECESNGTWDINTGNGFYGGVQFTLSSWQA 77

Qy         151 NGGSGSAANASREEQIRVAENVLRSQGIRAWPVCGRR 187
                || |    ||: |||: || :   ||  |||:| ::
Db          78 VGGEGYPHQASKAEQIKRAEILQDLQGWGAWPLCSQK 114
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This indicates that the structural features of SEQ ID NO: 2, including the regions spanning amino acids 117-184, are not significantly common to the single other sequence, SEQ ID NO: 36, that was evaluated for the recited required function. There is no showing that purified or non-purified polypeptides from *M. leprae, Streptomyces rimosus, M. smegmatis, M. bovis,* and *Corynebacterium glutamicum* are 95% identical to SEQ ID NO: 2 and have the required functions including the ability to resuscitate dormant, moribund or latent *M. tuberculosis* cells, as recited. Therefore, the resuscitating function has not been definitively correlated to structural features common to even a single other member of the genus tested. The structural features of species constituting a substantial portion of the genus are not disclosed. Clearly, the variations within the encompassed polypeptide genus are huge. Other than a purified SEQ ID NO: 2 which has been shown to have a capacity to resuscitate dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a culture medium upon contacting and incubating with the cells, no other polypeptide variants having at least 95% sequence identity to SEQ ID NO: 2 and concurrently having the functional capacity to resuscitate dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a culture medium or a human or animal sample and/or having the ability to identify a dormant, moribund or latent *M.*

tuberculosis cell in the sample by detecting growth of bacterial cells in the sample, have been adequately described, and their structure correlated with the requisite functions. The description of a single species having the required function within the recited broad genus is not be sufficient to support the patentability of the genus under 35 U.S.C § 112, first paragraph. See *University of California v. Eli Lilly & Co.*, 119 F.3d 15559, 1567, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). The instant specification does not disclose which 5% of amino acid residues should be changed within the single disclosed polypeptide species of SEQ ID NO: 2 in order to maintain the required biological functions, i.e., the functional capacity to resuscitate dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a culture medium or a human or animal sample, upon performing the recited steps and/or having the ability to identify a dormant, moribund or latent *M. tuberculosis* cell in the sample by detecting growth of bacterial cells in the sample. Given that the regions consisting of amino acids 117-184 in SEQ ID NO: 2 and SEQ ID NO: 36 are structurally so dissimilar or different, there is no definitive correlation of this region to the recited two requisite functions. Note that the Rpf or the Rpf2 used in the experiment of Figure 10 does not consist of amino acids 117-184 from SEQ ID NO: 2, but comprises other amino acid residues on both sides of amino acids 117-184, which amino acid residues may potentially be contributing to one or both of the requisite functions. Given the very diverse structure of *M. luteus* Rpf polypeptide compared to SEQ ID NO: 2, there is no predictability that a representative number of purified or non-purified polypeptides having up to 5% amino acids altered within or outside of amino acid residues 117-184, would retain the two requisite functions recited in the instant claims.

The Applicants' statement that one of skill in the art would expect that proteins having a higher degree of identity to SEQ ID NO: 2 would also promote

the growth of dormant cells, is contrary to what is recognized in the state of the art. For instance, Skolnick *et al*. (*Trends in Biotechnology* 18: 34-39, 2000) taught that a skilled artisan is well aware that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of proteins (see abstract; and page 34). Skolnick *et al*. further taught that even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see abstract and Box 2). In the instant application, other than the purified SEQ ID NO: 2, the only other purified polypeptide species that was in Applicants' possession at the time of the invention and that was tested for the recited resuscitating function was Rpf of *M. luteus*, having a dissimilar overall structure that is not 95% identical to SEQ ID NO: 2. Clearly, there is lack of adequate description of the structure of a representative number of at least 95% identical polypeptide variant species having the requisite functions.

With respect to the written description requirement, while 'examples explicitly covering the full scope of the claim language' typically will not be required, a sufficient number of representative species must be included 'to demonstrate that the patentee possesses the full scope of the [claimed] invention'. *Lizardtech, Inc. v. Earth Resource Mapping, Inc*., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). In the instant case, Applicants' specification does not contain adequate written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed. The instant specification mentions of polypeptide variant having at least 95% identity to the amino acid sequence of SEQ ID NO: 2. It should be noted that written description requires more than a mere statement that

something is a part of the invention. The specification does not disclose a correlation between the function, i.e., capacity to resuscitate dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a culture medium or a human or animal sample upon performing the recited steps and/or having the ability to identify a dormant, moribund or latent *M. tuberculosis* cell in the sample by detecting growth of bacterial cells in the sample, and the precise structure(s) responsible for those functions such that the skilled artisan would have known what modifications, substitutions, or variations could be made of the large number of modifications or variations currently encompassed within the scope of the instant claims, without losing those functions. This description is important because a change of even a single amino acid residue can alter the folding or conformation of a polypeptide such that the functional region no longer retains the function(s). Applicants only speculated that the cell wall lytic activity is 'likely' to be important for resuscitating dormant, moribund or latent bacterial cells. See paragraph bridging pages 13 and 14 of Applicants' amendment filed 08/01/07 and paragraph bridging pages 17 and 18 filed 10/16/08. The specific regions or amino acid residues within the amino acids spanning 117 to 184 of SEQ ID NO: 2 (all of which are absent in the Rpf polypeptide of *M. luteus*) that are associated with the alleged capacity to resuscitate dormant, moribund or latent *M. tuberculosis* bacterial cells *in vitro* in any sample or a sample from a human or animal, are not identified, without which one of skill in the art would not be able to avoid alterations or substitutions in those regions, or among amino acid residues within positions 117 to 184 of SEQ ID NO: 2, while producing species falling within the currently recited broad genus. A domain that includes four conserved tryptophan residues and two conserved cysteine residues which 'may' form a disulfide bridge (page 51, line 28 to page 52, line 2 of the specification) is not associated with the recited function of

resuscitating and/or identifying dormant, moribund or latent *M. tuberculosis* bacterial cells. Even if one produced a series of polypeptide variants falling within the scope of the recited sequence identity and used them to contact dormant, moribund or latent *M. tuberculosis* cells *in vitro* in a human or animal sample, there is no predictability that these polypeptide variants would retain the capacity to resuscitate said dormant, moribund, or latent bacterial *M. tuberculosis* bacterial cells and/or the ability to identify a dormant, moribund or latent *M. tuberculosis* cell in the sample by detecting growth of bacterial cells in the sample, absent a concrete structure-function correlation. As set forth previously, this is critically important because the state of the art at the time of the invention was limited to certain unsubstantiated or unproven speculations with regard to the potential use of Rpf-like proteins in detection of a bacterial cell (or diagnosis), treatment, and prophylaxis. For instance, Mukamolova *et al*. (*PNAS* 95: 8916-8921, July 1998, of record) (Mukamolova *et al*., 1998) stated that it was 'tempting to speculate' that resuscitation and growth of the very significant re-emerging pathogen *Mycobacterium tuberculosis* and possibly of *Mycobacterium leprae* 'may be' controlled in part at least by members of a family of secreted Rpf-like proteins that function as autocrine and/or paracrine growth factors. See last paragraph in left column on page 8921 of Mukamolova *et al*. (1998). In July 1998, Mukamolova *et al*. concluded as follows [Emphasis added]:

> **Further experimental work will be required to explore these hypotheses**, which may lead, in the short term, to substantially improved laboratory methods **for the detection** and cultivation of these organisms and in the longer term, to therapeutic strategies and vaccines for preventing their growth *in vivo*.

Applicants have advanced no arguments with regard to the Office's citation of the teachings of Mukamolova *et al*. (1998). Clearly, Applicants did not describe the invention of the instant claims adequately to show that they had possession of the

claimed method that uses the recited broad genus of polypeptide variants. See e.g., *Noelle v. Lederman*, 355 F.3d 1343, 1348, 69 USPQ2d 1508, 1513 (Fed. Cir. 2004) ('invention is, for purposes of the written description inquiry, *whatever is now claimed*'). Applicants should note that written description requires more than a mere statement that something is a part of the invention and a reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Without a structure-function correlation, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ….. does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is'). The instant claims are viewed as not meeting the written description provision of 35 U.S.C. § 112, first paragraph. The rejection is maintained.

Rejection(s) under 35 U.S.C § 112, First Paragraph

19) The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

20) Claims 128, 144, 159 and 162-164 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 128, as amended, includes the limitations: 'said bacterial cell is' present in a sample and the method 'identifies a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in the sample by detecting growth of bacterial cells in the sample'. Claim 128 depends from the amended claim 126, which requires the steps of contacting the dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells with an isolated polypeptide as recited and incubating the cells in culture medium containing the polypeptide, thereby resuscitating said bacterial cells. Thus, the *method of resuscitating* dormant, moribund or latent *Mycobacterium tuberculosis* cells comprising contacting the dormant, moribund or latent *Mycobacterium tuberculosis* cells present in a sample *in vitro* and incubating the cells in culture medium containing the polypeptide is required to serve also as a *method of identifying* specifically 'a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in the sample by detecting growth of bacterial cells in the sample' in the amended claim 128. Note that the sample recited in claim 128 encompasses a sample taken from a human or animal as recited in the dependent claim 159. New dependent claim 162, as amended, includes the limitations: 'said bacterial cells are present in a sample' and the method 'identifies a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in the sample by detecting growth of bacterial cells in the sample'. Claim 162 depends from the new claim 160 or 161, which requires the steps of contacting the dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells with a purified polypeptide as recited and incubating the cells in culture medium containing the polypeptide, thereby resuscitating said bacterial cells. Thus, the *method of resuscitating* dormant, moribund or latent *Mycobacterium tuberculosis*

cells comprising contacting the dormant, moribund or latent *Mycobacterium tuberculosis* cells present in a sample *in vitro* and incubating the cells in culture medium containing the polypeptide is required to serve also as a *method of identifying* specifically 'a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in the sample by detecting growth of bacterial cells in the sample' in the new claim 162. The resuscitating method of claims 144, 163 and 164 requires contacting *Mycobacterium tuberculosis* bacterial cells *in vitro* with a cell 'strain' expressing a nucleic acid encoding the recited polypeptide. Applicants do not point to specific parts of the as-filed specification that support the new claims, but point to Figure 1A, 1B, lines 11-15 of page 8 for the amendment made to claim 128. However, these parts of the specification do not provide descriptive support for a method of resuscitating dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells comprising the recited contacting and incubating steps which method concurrently serves also as a method of specifically *identifying* a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in said sample *by detecting* growth of bacterial cells in a human or animal sample. A generic cell 'strain' expressing a nucleic acid encoding the recited polypeptide has no support. Note that 'a cell strain' broadly encompasses a eukaryotic cell strain, a parasitic cell strain etc. Therefore, the identified limitation(s) in the claim(s) and the currently claimed scope of the claims constitute new matter. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific pages and lines of the disclosure, as originally filed, for the limitation identified above, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

21) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

22) Claims 128, 144, 159 and 162 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 128, as amended, is indefinite, inconsistent, confusing and/or lacks antecedent basis in the singular and/or pleural limitations 'bacterial cell …. in a sample' (see lines 1 and 2) and 'bacterial cells in the sample' (see lines 3 and 4). Claim 128 depends from claim 126, wherein what are resuscitated are dormant, moribund or latent *Mycobacterium tuberculosis* 'cells'. For proper antecedence and for the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the above-identified limitations with the limitations --bacterial cells …. in a sample-- in lines 1 and 2 and --said bacterial cells in the sample-- in lines 3 and 4 of the claim.

(b) Analogous rejection and criticism apply to claim 144, as amended, with regard to the limitation: incubating 'the bacterial cell'. Note that what are resuscitated (see line 2) are dormant, moribund or latent *Mycobacterium tuberculosis* 'cells'.

(c) New claim 162 is indefinite because it lacks sufficient antecedent basis in the limitation 'bacterial cells in the sample' (see line 3). Are these any generic bacterial cells, or the earlier recited dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in the sample? Note that the limitations 'bacterial cells' and 'dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells' are not of same scope.

(d) New claim 162 is indefinite and confusing in the limitations: 'the method identifies dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells in the sample by detecting growth of bacterial cells in the sample'. Claim 162 depends from claim 160 or 161, which includes contacting the dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cells with the purified polypeptide recited therein and incubating the cells in culture medium containing the polypeptide in order to resuscitate said cells. It is unclear how a *method of resuscitating* dormant, moribund or latent *Mycobacterium tuberculosis* cells comprising contacting the dormant, moribund or latent *Mycobacterium tuberculosis* cells present in a sample *in vitro* and incubating the cells in culture medium containing the polypeptide ends up being a *method of identifying* specifically 'a dormant, moribund or latent *Mycobacterium tuberculosis* bacterial cell in the sample by detecting growth of bacterial cells in the sample'.

(e) Analogous rejection and criticism apply to claim 128, as amended.

(f) Claim 159, which depends from claim 128, is also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

23) Claims 125-128, 131, 144, 150, 157, 159 and 161-164 stand rejected. Claim 160 contains allowable subject matter.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA and CANADA) or 571-272-1000.

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's acting supervisor, Patricia Duffy, can be reached on (571) 272-0855.

/S. Devi/
Primary Examiner
AU 1645

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